REPORT

Should blood donors be routinely screened for irregular antibodies?

M.A. García, L. Bautista, and F. Palomino

Alloantibody reactivity is approximately 0.3 percent in blood donors worldwide. The present study established total alloantibody and clinically significant alloantibody (CSAA) frequencies in all Colombian Red Cross National Blood Bank donors (almost all donors were Colombian). The probability of these alloantibodies reacting with a specific antigen in the general population was also determined, focusing on male CSAA data because routine practice in this blood bank is to discard female plasma components to avoid transfusion-related acute lung syndrome. Total blood donor population between 2007 and 2009 was 60,309 (55.4% male and 44.6% female). Cells I and II were used for alloantibody screening following the Autovue protocol. Positive samples were identified by red blood cell (RBC) panels (Panel A, Panel B, and Panel C, Ortho Clinical Diagnostics, Raritan, NJ). Alloantibody and CSAA frequency were established for both sexes. The database for RBC antigens estimated for the Colombian population was used for calculating the probability of antigen-antibody reaction from donors in this blood bank. Total alloantibodies (438) and CSAA frequency (138) were significantly higher in women than men ($p < 0.01$). Seventy-four percent of CSAA found in women came from the Rh blood group system. Calculated probability of generating antigen-antibody reaction using plasma only from male donors was estimated as 20.55 episodes for every 100,000 donations, and the probable number of events per year was 1.48. Meanwhile, considering all blood components from male and female origin, the calculated probability of antigen-antibody reaction was 123.54 episodes for every 100,000 donations and 28.67 probable events per year. The data presented here do not represent strong support for the routine screening of alloantibodies in blood donors. ***Immunohematology* 2012;28:60–6.**

Key Words: blood donor, alloantibody screening, alloantibody identification, blood bank, blood recipient

Blood component transfusion can produce a series of immunologic effects, the most serious ones being alloimmunization, allergic reactions, febrile reactions, and immunosuppression.[1–3] Red blood cell (RBC) antigen immunogenicity is the likelihood of an antibody being generated in a blood recipient. It depends on exposure route, the recipient's medical condition (inflammation, immunosuppression),[4] and history of previous alloimmunization (which promotes new alloimmunization).[5,6] Once exposed to an antigen, the immune system can develop antibodies, called *regular* when they are generated against the antigens of the ABO blood group system and *irregular* or *alloantibodies* (AAs) when they are generated against other RBC blood group systems.[7]

AA screening is a test performed by blood banks and transfusion services for reducing minor incompatibility.[7] AA seroprevalence in blood donors around the world has been estimated as being 0.3 percent (0.2%–0.8%).[7] Some reports from Latin America have shown similar values: 0.19 percent[8] in Costa Rica and 0.34 percent in Brazil.[9] Colombian regulations[10,11] make this test mandatory for all units of blood collected, without taking prevalence in national blood donors into account.

A previous study on a Colombian population[12] found 0.39 percent RBC AA prevalence, almost half of which were considered clinically significant alloantibodies (CSAAs) because they were related to hemolytic transfusion reactions (HTR) or shortened RBC survival.[12,13] The CSAAs found, in order of frequency, were anti-D, -E, -K, -M, -S, and -k. On the other hand, a 1993 study of 30,259 men involved in paternity suits from all regions of Colombia[14] documented RBC antigen prevalence for the eight most frequent blood group systems; the authors concluded that RBCs presented a predominantly Caucasian phenotype. Likewise, the Colombian National Institute of Health issued a consolidated report in 1999 regarding 338,063 blood units that were classified for ABO and D blood group antigens.[15] Both series are summarized in Table 1.

The present paper has two components: the first is a description of RBC AA frequency in Colombian Red Cross National Blood Bank (CRCNBB) blood donors in Bogota (2007–2009). A selection of CSAAs was also taken and organized by sex. The second component is the calculation of the likelihood of generating HTR or reduced RBC survival, using data from Table 1.

Study Design and Methods

Study Population

Total donations received between 2007 and 2009 were 60,309 (55.4% male and 44.6% female).

Table 1. Relevant red blood cell antigen frequency found in Colombian males and Colombian blood donors*

System	Phenotype	Frequency in males (%)	Frequency in blood donors (male and female) (%)
ABO (ISBT 001)	A	26.86	26.00
	B	9.24	7.30
	AB	1.83	1.40
	O	60.65	56.20
Rh (ISBT 004)	D	94.18	91.16
	CCdEE	0.00	
	CCdEe	0.00	
	CCdee	0.01	
	CcdEE	0.00	
	CcdEe	0.01	
	Ccdee	0.38	
	ccdEE	0.00	
	ccdEe	0.17	
	ccdee	5.19	
Kell (ISBT 006)	K+k–	0.06	
	K+k+	3.63	
	K–k+	96.29	
Duffy (ISBT 008)	Fy(a+b–)	30.86	
	Fy(a+b+)	39.04	
	Fy(a–b+)	26.61	
	Fy(a–b–)	3.46	
Kidd (ISBT 009)	Jk(a+b–)	26.52	
	Jk(a+b+)	42.66	
	Jk(a–b+)	29.24	
	Jk(a–b–)	1.56	

*Data obtained from Sandoval C et al.[14] and Beltran M et al.[15]

Screening Assay and RBC AA Identification

A retrospective search was conducted for whole-blood donations made between January 2007 and July 2009 to establish RBC AA prevalence in our donor population. AA screening was done using the Autovue system with the column agglutination method (polyclonal anti-IgG -C3d) and a 2-cell screen (Surgiscreen, Ortho Clinical Diagnostics, Raritan, NJ). AAs were identified in units having positive AA screening, using panels (Panel A, Panel B, and Panel C, Ortho Clinical Diagnostics). The following AAs were identified using those panels: anti-Le^a, -Le^b, -D, -C, -c, -E, -e, -Fy^a, -Fy^b, -K, -k, -Jk^a, and -Jk^b.

Nomenclature

We defined the following terms:

- Alloantibodies against low-prevalence antigens: those with a positive screening test but having a negative identification test result with panel A.
- Cold antibodies (CAs): antibodies reactive below 37°C.
- Nonspecific IgG antibodies (NIAs): those units having a positive screening test and complete agglutination in all cells from panel A.
- Non–clinically significant alloantibodies (NCSAAs): those not related to disease, HTR, or reduced RBC survival.
- Minor incompatibility: hemolysis after destroying a percentage of the patient's RBCs by antibodies present in a plasma unit.

Calculating Minor Incompatibility Likelihood for a Single Transfusion

The likelihood of generating an antibody-antigen reaction in a single plasma transfusion from male donors was established using RBC antigen frequencies estimated previously for Colombian people[14] and the frequency of AAs found in our blood donors. This calculation was performed using only male donors because our standard practice is to discard female fresh-frozen plasma units without taking into account the donor's history of pregnancies to reduce the incidence of transfusion-related acute lung injury (TRALI).[16,17] International reports suggest a 10 to 20 percent prevalence of antibodies to leukocyte antigens in female blood donors with a history of pregnancy and 1 to 5 percent in male donors as the main risk factor for TRALI (odds ratio, 15),[16] but it is not a regular practice in CRCNBB to perform leukocyte antibody screening. Moreover, as the demand for plasma components can be met with only male donors, this is a standard CRCNBB policy. Antigen-antibody reaction probability was calculated as being the likelihood of finding an AA in plasma donors and the corresponding RBC antigen in the recipient. Calculations were made as follows: the found antibody frequency was divided by the total number of donors, and the result was then multiplied by 100,000 transfusions to yield the antibody probability. Antigen-antibody reaction probability was calculated by multiplying antibody probability by 100,000 transfusions to yield the antigen likelihood in the population. The antigen probabilities we used in this calculation were those in Table 1.

Statistics

The χ^2 test was used to determine the significance of sex-related AA frequency with a significance level of 95 percent. AAs and RBC antigens are expressed as percentages of the total population.

Results

During the period being studied (2007–2009) there were 60,309 whole-blood donations, and 438 AAs were found (0.73%), 66.7 percent of them in female blood donors and 33.3 percent in male donors. The CSAAs were 140 (31.96%) and NCSAAs were 300 (68.5%) of those identified. Our results showed that the three AAs most frequently found in blood donors corresponded to NCSAAs; the most common AA found in blood donors (anti-Le^a) had similar sex distribution, as did anti-S (not significant). The other AAs had a clear tendency to be more prevalent in women, most of them being classified as CSAAs, such as anti-D or -C (Table 2).

Table 2. The frequency of alloantibodies in the donor population and their relationship to sex

Alloantibody	Number	% Total	Females	% F*	Males	% M*	p value
Anti-Le^a	137	31.28	68	49.64	69	50.36	
AALFAs	73	16.67	48	65.75	25	34.25	<0.1
Cold antibodies	61	13.93	34	55.74	27	44.26	
Nonspecific IgG	13	2.97	11	84.62	2	15.38	<0.1
Anti-Le^b	14	3.20	8	57.14	6	42.86	
Anti-D†	53	12.10	50	94.34	3	5.66	<0.05
Anti-E†	25	5.71	20	80.00	5	20.00	<0.05
Anti-K†	23	5.25	13	56.52	10	43.48	
Anti-M†	13	2.97	6	46.15	7	53.85	
Others†	26	6.0	22	100.00	4		<0.001
Total	438	100.00	280	63.93	158	36.07	<0.05

*F = female; M = male.

†Indicates alloantibodies considered clinically significant alloantibodies. The probability value represents the difference by sex.

AALFA = alloantibodies against low-prevalence antigens.

There were 12 cases in which two AAs were found in the same donor during the period being studied. Six of them were male donors having the following combinations: one anti-Le^a/CA; three anti-Le^a,-Le^b; one anti-Le^a/NIA, and one anti-Le^a, -Jk^a. Six female donors had the following combinations: three anti-D,-C, one anti-c,-E, and two anti-D,-E. It is worth noting that all AAs found in these women belonged to the Rh blood group system (ISBT 004).

Probability of Generating Antigen-Antibody Reaction in a Recipient

Tables 3 to 5 present the calculated probability of an antigen-antibody reaction, using fresh-frozen plasma (male donors only), platelets, and cryoprecipitate, respectively.

Discussion

Screening for AAs in every blood donor is mandatory for all Colombian blood banks but not in countries such as the Netherlands, United Kingdom, or United States.[7,18,19] In these countries there is a policy of specific screening in certain populations considered at risk, such as multiply-transfused patients or intrauterine transfusions. Although not required, most if not all blood centers in the United States are routinely screening blood donations for serum or plasma AAs. This may be because U.S. donor centers try to identify those donors having AAs of high enough titer for use in typing antisera in serologic investigations. The supposed aim of mandatory screening in Colombia, according to the regulations,[10,11] is to reduce the risk of AAs that may potentially cause early and delayed HTR in blood recipients, as well as shortened RBC survival. However, the evidence for serious adverse outcomes resulting from the transfusion of AAs other than ABO and Rh blood group antibodies contained in donor units to individuals that would, by chance, have the corresponding antigen(s) is lacking in the literature. Additionally, one has to consider that after transfusion these AAs would be diluted, making it unlikely that they would cause the recipient a detectable problem (Tables 3–6). Also, it is important to take into account that most if not all blood is now transfused as RBCs, having very little plasma.

The results in our donor population showed a 0.70 percent AA prevalence, which is higher than other reports.[7,8,9,13] Of the AAs reported, a third (0.2%) were considered CSAAs (anti-D, -C, -c, -E, -M, -S, -Fy^a, -Fy^b, -Jk^a, and -Jk^b).[12,13] As expected, in female donors the AA frequency was three times as high as in males,[7,20] mainly reflecting the presence of anti-D. Previous results have shown that RBC AA origin is related to history of previous transfusions and pregnancy.[13,20] Likewise, 80 percent of CSAAs were found in female donors; 65% of them belonged to the Rh blood group.[21,22]

Similarly, anti-K was the third CSAA found in our blood donor population; there was no statistical significance between sexes in frequency. This AA is the primary cause of hemolytic disease of the newborn (HDN) and HTR in other countries.[23–25] Nevertheless, the estimated frequency of dominant homozygous and heterozygous phenotypes in Colombia is close to 3.7 percent.[14] That is, we found a frequency of 3.8 cases per 10,000 patients for every unit transfused, which together with the previous considerations about the antigen-antibody reaction reinforces the low probability of experiencing these events. On the other hand, anti-M is rarely associated with HDN or HTR,[26,27] even when its expression

Table 3. Estimated probability of antigen-antibody reaction based on 60,309 donations screened for alloantibodies, using plasma only from only male donors for calculations

AA	Number of tested units	Ab frequency × 100,000 units	Ag probability per 100,000 Colombian inhabitants	AAR probability × 100,000 units	Probable number of events per year	Units required for generating 1 AAR	Cases per year
Anti-D	7152	4.97	0.9421	4.69	0.34	21,338	1 each 2.98 years
Anti-K	7152	16.58	0.0369	0.61	0.04	163,439	1 each 22.85 years
Anti-E	7152	8.29	0.4132	3.43	0.25	29,191	1 each 4.08 years
Anti-M	7152	11.61	0.8653	10.04	0.72	9957	1 each 1.39 years
Anti-S	7152	3.32	0.5372	1.78	0.13	56,133	1 each 7.85 years
Total				20.55	1.48		

AA = alloantibody; Ab = antibody; Ag = antigen; AAR = antigen-antibody reaction.

Table 4. Estimated probability of antigen-antibody reaction based on 60,309 donations screened for alloantibodies, using platelets from both male and female donors

AA	Number of tested units	Ab frequency × 100,000 units	Ag probability per 100,000 Colombian inhabitants	AAR probability × 100,000 units	Probable number of events per year	Units required for generating 1 AAR	Cases per year
Anti-D	5228	87.88	0.9421	82.79	4.33	1208	1 each 0.23 years
Anti-K	5228	38.14	0.0369	1.41	0.07	71,060	1 each 13.59 years
Anti-E	5228	41.45	0.4132	17.13	0.9	5838	1 each 1.11 years
Anti-M	5228	21.56	0.8653	18.65	0.98	5361	1 each 1.02 years
Anti-S	5228	6.63	0.5372	3.56	0.19	28,066	1 each 5.37 years
Total				123.54	6.47		

AA = alloantibody; Ab = antibody; Ag = antigen; AAR = antigen-antibody reaction.

Table 5. Estimated probability of antigen-antibody reaction based on 60,309 donations screened for alloantibodies, using cryoprecipitate from both male and female donors

AA	Number of tested units	Ab frequency × 100,000 units	Ag probability per 100,000 Colombian inhabitants	AAR probability × 100,000 units	Probable number of events per year	Units required for generating 1 AAR	Cases per year
Anti-D	1317	87.88	0.9421	82.79	1.09	1208	1 each 0.92 years
Anti-K	1317	38.14	0.0369	1.41	0.02	71,060	1 each 59.95 years
Anti-E	1317	41.45	0.4132	17.13	0.23	5838	1 each 4.44 years
Anti-M	1317	21.56	0.8653	18.65	0.25	5361	1 each 4.07 years
Anti-S	1317	6.63	0.5372	3.56	0.05	28,066	1 each 21.31 years
Total				123.54	1.64		

AA = alloantibody; Ab = antibody; Ag = antigen; AAR = antigen-antibody reaction.

Table 6. Estimated probability of antigen-antibody reaction based on 60,309 donations screened for alloantibodies, using red blood cell units from both male and female donors

AA	Number of tested units	Ab frequency × 100,000 units	Ag probability per 100,000 Colombian inhabitants	AAR probability × 100,000 units	Probable number of events per year	Units required for generating 1 AAR	Cases per year
Anti-D	23,204	87.88	0.9421	82.79	19.21	1208	1 each 0.05 years
Anti-K	23,204	38.14	0.0369	1.41	0.33	71,060	1 each 3.06 years
Anti-E	23,204	41.45	0.4132	17.13	3.97	5838	1 each 0.25 years
Anti-M	23,204	21.56	0.8653	18.65	4.33	5361	1 each 0.23 years
Anti-S	23,204	6.63	0.5372	3.56	0.83	28,066	1 each 1.21 years
Total				123.54	28.67		

AA = alloantibody; Ab = antibody; Ag = antigen; AAR = antigen-antibody reaction.

begins in erythroid precursors.[26] The global frequency of M is 75 percent; hence, 25 percent of the population lacks M; such individuals are able to generate anti-M when they are exposed to the antigen. However, the frequency of anti-M was only 0.02 percent in this population, reflecting perhaps a low immunogenic power of this antigen.

Regular Antibodies Compared With Irregular Antibodies

Old transfusion practices used whole blood from universal group O donors, and the regular antibodies in the plasma fraction of whole blood usually were not associated with significant antigen-antibody reactions. It would thus be inconsistent to think that an irregular antibody having a lower serum concentration than a regular antibody can produce transfusion reactions in a recipient, given the percentage of plasma present in a unit of RBCs (which is less than 5%[28] and is diluted in preservative solution), which is the most transfused component. Otherwise, transfusion of group O blood to group A or B patients would be considered unacceptable.[29] Although these antibodies are transfused, they can adsorb to antigens located in different organs (e.g., endothelium, liver) because their expression is not limited to RBCs, reducing the chances of HTR or exposure to circulating RBCs.

To test this hypothesis, a study was conducted that determined regular antibodies' agglutination capacity in supernatant from packed RBC units obtained from our blood bank. We were unable to demonstrate any agglutination despite including an indirect antiglobulin test for regular antibodies in the RBC supernatant whose ABO groups were known (data not shown). The data shown in Tables 3 to 5 reflecting calculations of the probability of antigen-antibody reaction, along with the traditional practice of transfusion, showed a low probability as a result of transfusion of plasma components, as has been shown in other studies.[30–32] Then, even if transfused (fresh-frozen plasma, RBC units, platelets, or cryoprecipitates), these antibodies will be unlikely to cause recipient hemolysis because they will be diluted in the recipient's circulation.[33–36]

As shown in Tables 3 through 6, the likely number of antigen-antibody reactions per year was significantly higher in the calculations involving the components obtained from women than those from men. If the analysis is performed separately for men and women for the transfusion of RBC units (Table 6), the probable number of events per year for anti-D, -K, -E, -M, and -S is 23.99 cases per year (women) versus 4.68 cases per year (men). However, as mentioned previously, because the content of plasma in RBC units is very low and the dilution in the intravascular compartment is high, the overall effect may be negligible.

Special Considerations

With respect to the resistance to irregular antibody screening in platelet donors, it is necessary to emphasize that the problem of rejection and platelet alloimmunization is attributable mostly to the presence of anti-HLA antibodies, antineutrophil antibodies, and antiplatelet glycoprotein antibodies,[37] which are found in 30 percent of women not transfused but with a history of pregnancy,[38,39] and 66 percent of women with a history of transfusion and pregnancy.[40] Not all of them correspond to RBC antibodies, and therefore they are not routinely screened for in blood banks. Therefore, performing a routine RBC antibody screen is of little value. Additionally, although transfused plasma could have RBC antibodies, they are distributed throughout the available intravascular fluid and eventually join a fraction of these RBC receptors. However, because there is a much larger number of RBCs than RBC antibodies, the rate of antibody-antigen reaction is limited by the antibody provided, which has been processed at temperatures between 18° and 23°C, which reduces its activity.[41,42] Thus, the proposal to remove the screening of irregular antibodies will neither increase the number of cases of HTR nor reduce RBC survival in this population.

In emergency transfusion situations and massive transfusions such as patients with hemorrhagic shock who need immediate blood transfusion, there is no time for the blood bank to perform antibody screening tests; under these circumstances the risk of transfusing group O uncrossmatched RBCs is very low and is lower than the risk of the patient's death if a blood transfusion is delayed.[43]

These data, taken together with that presented by other authors,[7,12,13,18,19,44] demonstrated the low frequency of such AAs in the blood donor population and called into question this measure's usefulness regarding its cost as a routine procedure.

Conclusion

The data presented above do not represent strong support for the routine screening for AAs in blood donors. It is thus proposed that the Colombian blood donor population should not be subjected to routine AA screening; instead, we suggest that all Colombian blood banks adopt the Colombian Red Cross policy of discarding female plasma, thus withdrawing from the market four of five units that could theoretically contribute

to antigen-antibody reaction. AA screening in donors is only useful if the recipient's phenotype has been ascertained. This should only be done for those who need long-term blood transfusions and who clearly have high CSAA frequency.[44] AA screening is not clinically significant in patients who are only transfused once. Colombia is a country having limited resources, and public health assets should be adjusted to the population. Evidence-based strategies for redistributing existing resources should therefore be implemented. These would avoid annual resources being inappropriately used on screening that does not prevent HTR reactions or shortened RBC survival in 99.96 percent of cases.

References

1. Mincheff MS, Meryman HT, Kapoor V, Alsop P, Wötzel M. Blood transfusion and immunomodulation: a possible mechanism. Vox Sang 1993;65:18–24.
2. Mincheff MS, Meryman HT. Blood transfusion, blood storage and immunomodulation. Immunol Invest 1995;24:303–9.
3. Zimrin AB, Hess JR. Current issues relating to the transfusion of stored red blood cells. Vox Sang 2009;96:93–103.
4. Heal JM, Phipps RP, Blumberg N. One big unhappy family: transfusion alloimmunization, thrombosis, and immune modulation/inflammation. Transfusion 2009;49:1032–6.
5. Flegel WA. Immunogenicity reloaded. Blood 2009;114: 3979–80.
6. Tormey CA, Stack G. The characterization and classification of concurrent blood group antibodies. Transfusion 2009;49: 2709–18.
7. Initial detection and identification of alloantibodies to red cell antigens. Chapter 19. In: Brecher ME, Leger RM, Linden JV, Roseff SD. Technical manual. 15th ed. Arlington, VA: American Association of Blood Banks, 2005:423-53.
8. Villalobos J, Wittingham M, Vargas C. Anticuerpos irregulares contra eritrocitos en donantes del Banco Nacional de Sangre. [Irregular antibodies against red blood cells in blood donors.] http://www.hemasferio.com/src/img_up/GCIAMT/24.pdf. Accessed on August 20, 2010.
9. Posser N. Prevalencia de Anticorpos Irregulares em Doadores de Sangue do Hemocentro Regional de Passo Fundo-RS. [Prevalence of irregular antibodies in blood donors at regional blood bank of Passo Fundo-RS.] Available at: http://www.ulbracarazinho.edu.br/novo/grades/tcc%202008%202%20biomedicina/Nat%E1lia%20Posser%20Trentin.pdf. Accessed August 20, 2010.
10. Decreto 1571 de 1993. Por el cual se reglamenta parcialmente el Título IX de la Ley 09 de 1979, en cuanto a funcionamiento de establecimientos dedicados a la extracción, procesamiento, conservación y transporte de sangre total o de sus hemoderivados, se crean la Red Nacional de Bancos de Sangre y el Consejo Nacional de Bancos de Sangre y se dictan otras disposiciones sobre la materia. [Decree 1571 of 1993. Which regulates Title IX of Act 09 of 1979, in terms of operation of establishments engaged in the extraction, processing, preservation, and transportation of whole blood or its components, created the National Network of Blood Banks and National Council of Blood Banks and other provisions on the subject.] Available at: http://www.presidencia.gov.co/prensa_new/decretoslinea/1993/agosto/12/dec1571121993.pdf. Accessed January 13, 2010.
11. Resolución 901 1996. Manual de Normas Técnicas y Administrativas para Bancos de Sangre y Servicios de Transfusión. República de Colombia. Available at: http://190.27.195.165/index.php?idcategoria=80695#. [Resolution 901 1996. Manual of Standard, administrative and procedures for Colombian Blood Banks (In Spanish)] https://www.icbf.gov.co/transparencia/derechobienestar/resolucion/resolucion_minsalud_r0901_96.html. Accessed July 09, 2012.
12. Dueñas VH, Cortes A, Rovetto P, Neuta PA. Embarazo y transfusión y su asociación con aloanticuerpos inesperados de significancia clínica contra antígenos eritrocitarios. [Pregnancy and transfusion and its association with clinically significant alloantibodies against unexpected red cell antigens.] Colombia Med 1999;30:26–31. Available in: http://www.google.com.co/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&sqi=2&ved=0CFIQFjAA&url=http%3A%2F%2Fcolombiamedica.univalle.edu.co%2Findex.php%2Fcomedica%2Farticle%2Fdownload%2F118%2F119&ei=P5f7T9eWPO620AGuiMTVBg&usg=AFQjCNHLLcvPMtwTGkst0lq4oyyYkMQtOg. Accessed July 09, 2012.
13. Galel SA, Nguyen DD, Fontaine MJ, Goodnough LT, Viele MK. Transfusion medicine. In: Greer JP, Foerster J, Rodgers GM, et al., eds. Wintrobe's clinical hematology. 12th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2009:490–527.
14. Sandoval C, De la Hoz A, Yunis E. Estructura genética de la población Colombinana. [Genetic structure of the Colombian population.] Rev Fac Med Univ Nac Colomb 1993;41:3–14.
15. Beltrán M, Ayala M, Jara J. Frecuencia de grupos sanguíneos y factor Rh en donantes de Sangre, Colombia, 1996. [Frequency of blood groups and Rh factor in blood donors, Colombia, 1996.] Biomedica 1999;19:45–9.
16. Middelburg RA, van Stein D, Briët E, van der Bom JG. The role of donor antibodies in the pathogenesis of transfusion-related acute lung injury: a systematic review. Transfusion 2008;48:2167–76.
17. Eder AF, Benjamin RJ. TRALI risk reduction: donor and component management strategies. J Clin Apher 2009;24: 122–9.
18. Koelewijn JM, Vrijkotte TG, van der Schoot CE, Bonsel GJ, de Haas M. Effect of screening for red cell antibodies, other than anti-D, to detect hemolytic disease of the fetus and newborn: a population study in the Netherlands. Transfusion 2008;48:941–52.
19. Council of Europe. Guide to the preparation, use and quality assurance of blood components: recommendation No. R (95) 15. 10th ed. Strasbourg: Council of Europe Publishing, 1997.
20. Takeshita A, Watanabe H, Fijihara H, et al. Collaborative study of irregular erythrocyte antibodies in Japan: results from the Japanese study group of allo-immunity and antigen diversity in Asian populations. Transfus Apher Sci 2010;43:3–8.
21. Aygun B, Padmanabhan S, Paley C, Chandrasekaran V. Clinical significance of RBC alloantibodies and autoantibodies in sickle cell patients who received transfusions. Transfusion 2002;42:37–43.
22. McAdams RM, Dotzler SA, Winter LW, Kerecman JD. Severe hemolytic disease of the newborn from anti-e. J Perinatol 2008;28:230–2.

23. Lee S, Zambas ED, Marsh WL, Redman CM. The human Kell blood group gene maps to chromosome 7q33 and its expression is restricted to erythroid cells. Blood 1993;81:2804–9.
24. Marsh WL, Oyen R, Alicea E, Linter M, Horton S. Autoimmune hemolytic anemia and the Kell blood groups. Am J Hematol 1979;7:155–62.
25. Vaughan JI, Manning M, Warwick RM, Letsky EA, Murray NA, Roberts IA. Inhibition of erythroid progenitor cells by anti-Kell antibodies in fetal alloimmune anemia. N Engl J Med 1998;338:798–803.
26. Hinchliffe RF, Nolan B, Vora AJ, Stamps R. Neonatal pure red cell aplasia due to anti-M. Arch Dis Child Fetal Neonatal Ed 2006;91:F467–8.
27. De Young-Owens A, Kennedy M, Rose RL, Boyle J, O'Shaughnessy R. Anti-M isoimmunization: management and outcome at the Ohio State University from 1969 to 1995. Obstet Gynecol 1997;90:962–6.
28. van Rhenen DJ, Vermeij J, de Voogt J, Bernes JC, Payrat JM. Quality and standardization in blood component preparation with an automated blood processing technique. Transfus Med 1998;8:319–24.
29. Barjas-Castro ML, Locatelli MF, Carvalho MA, Gilli SO, Castro V. Severe immune haemolysis in a group A recipient of a group O red blood cell unit. Transfus Med 2003;13:239–41.
30. Sigler E, Shvidel L, Yahalom V, Berrebi A, Shtalrid M. Clinical significance of serologic markers related to red blood cell autoantibodies production after red blood cell transfusion-severe autoimmune hemolytic anemia occurring after transfusion and alloimmunization: successful treatment with rituximab. Transfusion 2009;49:1370–4.
31. Alarif L, Castro O, Ofosu M, Dunston G, Scott RB. HLA-B35 is associated with red cell alloimmunization in sickle cell disease. Clin Immunol Immunopathol 1986;38:178–83.
32. Tormey CA, Stack G. Immunogenicity of blood group antigens: a mathematical model corrected for antibody evanescence with exclusion of naturally occurring and pregnancy-related antibodies. Blood 2009;114:4279–82.
33. Giblett ER. Testing, testing. Arch Intern Med 1978;138:469.
34. Giblett ER. Blood group alloantibodies: an assessment of some laboratory practices. Transfusion 1977;17:299–308.
35. Mohn JF, Lambert RM, Bowman HS, Brason FW. Experimental transfusion of donor plasma containing blood-group antibodies into incompatible normal human recipients. I. Absence of destruction of red cell mass with anti-Rh, anti-Kell and anti-M. Br J Haematol 1961;7:112–29.
36. Bowman HS, Brason FW, Mohn JF, Lambert RM. Experimental transfusion of donor plasma containing blood group antibodies into incompatible normal human recipients. II. Induction of isoimmune haemolytic anemia by a transfusion of plasma containing exceptional anti-CD antibodies. Br J Haematol 1961;7:130–45.
37. Gottschall JL, Triulzi DJ, Curtis B, et al. The frequency and specificity of human neutrophil antigen antibodies in a blood donor population. Transfusion 2011;51:820–7.
38. Payne R. The development and persistence of leukoagglutinins in parous women. Blood 1962;19:411–24.
39. Densmore TL, Goodnough LT, Ali S, Dynis M, Chaplin H. Prevalence of HLA sensitization in female apheresis donors. Transfusion 1999;39:103–6.
40. [No authors listed]. Leukocyte reduction and ultraviolet B irradiation of platelets to prevent alloimmunization and refractoriness to platelet transfusions. The Trial to Reduce Alloimmunization to Platelets Study Group. N Engl J Med 1997;337:1861–9.
41. Endoh T, Kobayashi D, Tsuji N, et al. Optimal prewarming conditions for Rh antibody testing. Transfusion 2006;46: 1521–5.
42. Yamanishi H, Iyama S, Yamaguchi Y, Yanagihara T. The effect of reaction temperature for nephelometric assays for rheumatoid factor. Clin Chim Acta 2000;292:117–25.
43. Kaufman R. A fresh take on whole blood. Transfusion 2011; 51:230–3.
44. Campbell-Lee SA. The future of red cell alloimmunization. Transfusion 2007;47:1959–60.

Michel Andrés García, MD (corresponding author), Departamento de Fisiología, Universidad del Rosario, Carrera 24 No. 63C-69, Bogotá, Colombia; Leonardo Bautista, MD, Clinica Lorencita Villegas, Bogotá, Colombia; and Fernando Palomino MD, Scientific Adviser of the National Blood Bank of the Colombian Red Cross, Bogotá, Colombia.